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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/780,758	02/08/2001	Elaine Unemori	CONN-003CON	6616

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EXAMINER	
KAUFMAN, CLAIRE M	
ART UNIT	PAPER NUMBER
1646	4

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Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Application No.	Applicant(s)
09/780,758	UNEMORI, ELAINE
Examiner	**Art Unit**
Claire M. Kaufman	1646

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other

DETAILED ACTION

The preliminary amendment filed 2/8/01 has been entered with the following exception: the insertion after "Relaxin" at page 4, line 28 could not be made because that word does not appear on that line. It does appear on line 27, and if Applicant wishes the amendment to be made there, it should be corrected and resubmitted.

Examiner's note on amendment at page 6, line 22, replacing "treating depression" with –promoting angiogenesis--: While these are activities not necessarily related, the specification clearly supports substitution of the terms in the paragraph bridging pages 5-6 and on page 6, lines 15-18. Treatment of depression is not previously referred to in the specification, while promotion of angiogenesis is referred to multiple times. Therefore, it reasonably appears that reference to depression was an inadvertent error.

Claim Objections

Claim 28 is objected to because of the following informalities: in line 2, "stpes" should be –steps--; in line 3, the word "relaxin" is missing after "human". Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 23-27 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 6,211,147. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are both methods of treating a patient with recombinant human relaxin to obtain the same serum concentration from which one would reasonably expect the same therapeutic effect.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 23, 31 and dependent claims 24-27, 32 and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 23 is vague and indefinite because it is not clear what is being treated or what the effect is.

Claim 31 is indefinite because is not clear what "a period of up to at least 72 hours" means. That is, does it mean up to 72 hours or at least 72 hours.

Claim Rejections - 35 USC § 102

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 23, 24, 26, 28-32 and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Cronin et al. (US Patent 5, 166,191) in light of Applicant's admission.

Cronin et al. teach administering H2 human recombinant relaxin by osmotic pump to rats for at least 72 hours (see Figs. 5 and 6) at a does of 10ng/min (col. 18, lines 15-62). The predetermined rate of relaxin release was sequentially timed (col. 18, lines 52-54). The therapeutic effect was increased heart rate.

Applicant admits that relaxin induces VEGF secretion (*e.g.*, p. 5, lines 6-8). Therefore, the method of Cronin would inherently induce VEGF secretion as required by claims 28-32 and

34. Note that Applicant's admission is not relied upon in the rejection but only serves as evidence of the inherent effect of relaxin on VEGF secretion.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 23-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Bigazzi et al. (AI, US Patent 5,952,296) in view of Hudson et al. (AA, US Patent 5,023,321), Bryant-Greenwood (AM, Endocrin Rev., 1982, 3:62-90) and Wong et al. (US Patent 5,023,088) and Applicant's admission in the specification in Example 4.

Bigazzi et al. teach administration of relaxin to a human patient in an amount effective for dilation of blood vessels, relieving vascular dysfunctions, or relieving obliterative or obstructive peripheral arteriopathy (claim 1), as well as for relieving pre-eclampsia (claim 18) or circulatory and thrombo-ischemic diseases (col. 2, lines 42-48). Parenteral administration is taught as intraperitoneal injection (col. 6, lines 32-33). Background art discussed is the work of Bryan-Greenwood (discussed below), for the conclusion that "The availability of pure preparations of relaxin has always been quite limited due to the difficulty of isolating and purifying it, as well as the scarcity of organs from which to extract it" (col. 1, lines 19-23). However, the cloning of human relaxin by Hudson et al. (discussed below) is also noted as offering "new possibilities to finally research and understand the biology and the role of this hormone" (col. 1, lines 28-36). Bigazzi et al. do not specifically teach maintaining a serum concentration of at least 1ng/ml of relaxin, use of recombinant human relaxin (H2), administration by osmotic pump or at a progressively diminishing rate. Nor does Bigazzi et al. teach induction of VEGF secretion.

Hudson et al. teach making human recombinant relaxin H2 from cDNA clones, and that it was biologically active in a rat uterine contraction test (col. 13, line 46, through col. 17, line 28; see also claims 1-3).

Bryant-Greenwood states that for purification of natural relaxin, pregnant sow ovaries are hard to come by and while pregnant rats are not, rats are expensive to use because of the volume of ovaries needed for relaxin purification. It appears that relaxin freshly purified from ovaries has a high activity, but stability apparently decays over time. Also it is difficult to obtain a homogeneous purified preparation with consistent activity (beginning p. 46, middle of col. 2, though p. 65, middle of col. 2).

Wong et al. teach a multi-chamber osmotic pump (see, *e.g.*, claim 1, section c, and col. 4, lines 19-36) that allows function at a predetermined rate comprising sequentially timed dispensing (*e.g.*, col. 2, lines 33-39). This includes the ability for release at a diminishing rate (col. 16, lines 11-54, especially lines 40-50). Also taught are prior art multi-chamber osmotic pumps (col. 2, lines 10-18) and the dispensing of proteins such as hormones, including those produced recombinantly (col. 3, line 53 to col. 4, line 18).

Applicant admits that relaxin in a concentration as low as 1ng/ml stimulates VEGF secretion (sentence bridging pages 10-11).

It would have been obvious at the time the invention was made to one of ordinary skill in the art to administer relaxin by the method of Bigazzi et al. as taught for its healing properties related to circulatory vascular diseases and thrombo-ischemic diseases. It further would have been obvious to use recombinant human relaxin H2 in the method of treatment taught by Bigazzi et al. because purification of non-recombinant relaxin is costly, inconvenient, and generally results in a less than desirably homogeneity, as described by Bryant-Greenwood. Production of recombinant relaxin by the method of Hudson et al. would yield relatively inexpensive (an inherent property of recombinantly production of proteins), biologically active, and homogeneous human relaxin H2 without the potential of presence of infectious viruses. Bigazzi et al. provided motivation for use of recombinant relaxin by pointing out that it offered new possibilities to research the role of the hormone. Additionally, it was routine in the art to optimize drug delivery so delivery was directed most specifically in location and concentration for treatment with the drug. As a result of routine optimization and the teachings of Wong et al.

it would have been obvious to use an osmotic pump for release of relaxin in the method taught by Bigazzi et al., including a multi-chamber osmotic pump, one with a predetermined rate and a diminishing rate. Even though Bigazzi et al. is silent with respect to secretion of VEGF, because the claims have no upper limit for the amount that can be used, the amount effective in the methods claimed by Bigazzi et al. would reasonably have been expected to be effective in the instant claimed methods absent evidence to the contrary. One of ordinary skill would have expected an amount necessary to alleviate such major symptoms as vascular dysfunction as taught by Bigazzi would reasonably have been expected also to be effective for the method claimed in the instant application. The amount of 1ng/ml recited in the claims is within the range used by Bigazzi et al. (see claim 7, for example, of Bigazzi et al.) and was admitted by Applicants to induce VEGF secretion. Therefore, absent evidence to the contrary, the method of Bigazzi et al. would have necessarily lead to secretion of VEGF by relaxin at the amount administered by Bigazzi et al. The recitation of a newly discovered property inherently possessed by relaxin, that is the induction of VEGF secretion, does not make the administration of relaxin novel or unobvious. For these reasons, the invention as claimed is *prima facie* obvious. The claimed methods do not define over the prior art.

Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Cronin et al. (US Patent 5,478,807) is cumulative with the reference relied upon in the rejection under 35 UCS 102(b) above and teaches the same method of using H2 relaxin (Example 2).

Norrby et al. (AV, Int. J. Microcirc. Clin. Exp., 1996, 16(5):227-231), published the same year the priority application was filed, states that relaxin is not angiogenic. It is also stated by Norrby et al. (p. 228, middle of second paragraph) that the *in vivo* assay they used "is probably the only one by which de novo angiogenesis can be truly quantified in terms of even the smallest newly formed vessels in mammalian tissue which is natively vascularized."

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Thursday from 8:30AM to 12:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (703) 308-6564.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

Claire M. Kaufman, Ph.D.

Patent Examiner, Art Unit 1646

June 27, 2002